Amendments to the Specification:

Please replace the first paragraph (priority claim) which immediately follows the title on page 1 with the following amended paragraph:

This application is a continuation of Application 10/234,273, filed September 4, 2002, ~~pending~~ abandoned, which is a continuation of Application. 09/931,680, filed August 16, 2001, U.S. Patent. 6,468,968; which is a continuation of Application. 09/552,634, filed April 19, 2000, U.S. Patent. 6,306,825; which is a continuation of Application 09/350,560, filed July 9, 1999, abandoned; which is a divisional of Application 09/047,056, filed March 24, 1998, U.S. Patent. 5,977,066; which is a divisional of. Application 08/471,301, filed June 6, 1995, U.S. Patent. 5,759,997; which is a continuation of Application 08/163,193, filed December 6, 1993, U.S. Patent 5,639,724; which is a continuation of Application 07/940,119, filed September 3, 1992, abandoned; which is a continuation of Application 07/822,375, filed January 17, 1992, abandoned; which is a continuation of Application 07/481,082, filed February 16, 1990, abandoned.

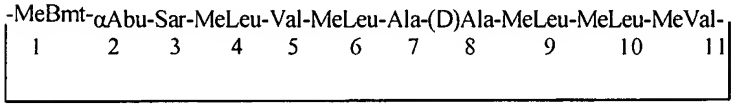
Please replace the first paragraph after the claim of priority on page 1 with the following amended paragraph:

The present invention relates to novel galenic formulations, in particular novel pharmaceutical compositions as well [[a]] as novel oral dosage forms comprising a cyclosporin as active ingredient.

Please replace the second paragraph after the claim of priority on page 1 with the following amended paragraph:

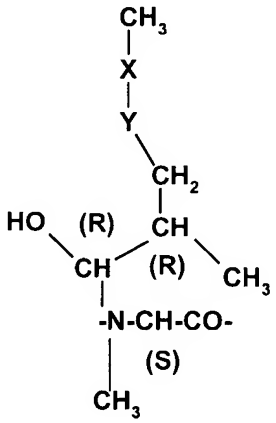
The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated ~~endecapeptides~~ undecapeptides, commonly possessing pharmacological, in particular

immunosuppressive, anti-inflammatory and/or anti-parasitic (in particular anti-protozoal, e.g. anti-malarial) activity. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or Cyclosporine, also known as cyclosporin A and commercially available under the Registered Trade Mark SANDIMMUN^R or SANDIMMUNE^R. Ciclosporin is the cyclosporin of formula A.



(A)

wherein –MeBmt- represents the N-methyl-(4R)-4-but-2E-en-l-yl-4-methyl-(L)threonyl residue of formula B



(B)

in which –x-y- is –CH=CH- (trans).

Please replace the last paragraph that begins on page 5 and ends on page 6 with the following amended paragraph:

First the palatability of the known oil based systems has proved problematic. The taste of the known drink-solution is, in ~~particualr~~ particular, unpleasant and admixture with an appropriate flavoured drink, for example chocolate drink preparation, at high dilution immediately prior to ingestion has generally been practiced in order to make regular therapy at all acceptable. Adoption of oil based systems hitherto has also required the use of high ethanol concentrations to maintain solubility. Use of ethanol is in itself inherently undesirable, in particular where administration to children is foreseen. In addition, evaporation of the ethanol, e.g. from encapsulated forms (adopted, in large part, to meet problems of palatibility as discussed above), or other forms (e.g. when opened) results in development of a precipitate. Where such compositions are presented in e.g. soft gelatin encapsulated form, this particular difficulty necessitates packaging of the encapsulated product in an air-tight compartment, for example in air-tight blister or aluminum-foil blister package or container. This in turn renders the product both bulky and more expensive to produce. The storage characteristics of such formulations are thus far from ideal.

Please replace the last paragraph on page 7 with the following amended paragraph:

Several proposals to meet these various problems have been suggested in the art, including both solid and liquid oral dosage forms. An overriding difficulty has however remained the inherent insolubility of the cyclosporins, e.g. Ciclosporin, in aqueous media

and hence provision of a dosage ~~from~~ which can contain cyclosporins in sufficiently high concentration to permit convenient use and yet meet the required criteria in terms of bioavailability, e.g. enabling effective resorption from the stomach or gut lumen and achievement of consistent and appropriately high blood/blood-serum levels.

Please replace the first paragraph on page 8 with the following amended paragraph:

As already noted, current commercial oral dosage forms for Ciclosporin are disclosed and claimed, e.g. in US patent no. 4,388,307. The early phase of this development is reflected in Swiss patent application no. 8634/78-8 which serves as a priority document to this patent. This application is directed to galenic formulations comprising Ciclosporin as the active ingredient together with a carrier medium comprising any one or more of the following components:

i) sesame oil;

ii) a non-ionic tenside, e.g. Tween 80, Cremophore EL, 40 or 60 or lecithins;

iii) a trans-esterified non-ionic triglyceride, e.g. Labrafil;

iv) mixtures of a lecithin (e.g. Epikuron), ingredients (iii) and ethyloleate;

v) neutral oils, e.g. saturated C_{8-12}triglycerides such as Miglyol 812; and

vi) mono- and/or di-glycerides such as glycerol monooleate, glycerol monostearate and clycerol distearate.

Please replace the last paragraph on page 10 with the following amended paragraph:

In accordance with the present invention, it has now surprisingly been found that pharmaceutical compositions comprising cyclosporins, in particular Ciclosporin, as active ingredient, which meet or substantially reduce difficulties in dosaging and patient acceptability hitherto encountered in the art, e.g. as discussed above, can be achieved

by the use of carrier systems comprising fatty acid tri-glycerides and mono-/di-glycerides, suitably in combination ~~a conjunction~~ with a hydrophilic tenside. In particular, it has been found that, employing the defined carrier systems, it is possible to obtain oil-based compositions, which are not aqueous emulsions, and which do not require the presence of additional solvents, co-solvents or solubilizers, for example ethanol or Labrafils or the like, and which exhibit high stability as well as improved bioavailability characteristics as compared with known cyclosporin/fatty acid triglyceride/solvent/co-solvent systems, for example, the known Sandimmun^{R} drink-solution. In a specific aspect the present invention provides for oil-based pharmaceutical compositions, in particular oil-based pharmaceutical compositions other than aqueous emulsions, which are free or substantially free of ethanol.

Please replace the second paragraph on page 11 with the following amended paragraph:

By closer standardisation of individual patient dosaging rate and blood/blood-serum level response, as well as dosaging and response ~~para~~ parameters for patient groups, monitoring requirements may be reduced, thus substantially reducing the cost of therapy.

Please replace the third complete paragraph on page 12 with the following amended paragraph:

Component (a) in the compositions of the invention may be any therapeutically applicable cyclosporin, e.g. as hereinbefore indicated. ~~the~~ The preferred component (a) in the compositions of the invention is Ciclosporin. A further preferred component (a) in the compositions of the invention is [Nva]^{2}-Ciclosporin, also known as cyclosporin G.

Please replace the last complete paragraph on page 13 with the following amended paragraph:

Such trans-esterification products [ingredients (b+c)] are generally obtained by heating of the vegetable oil, e.g. corn oil, with glycerol, propylene glycol or sorbitol [e.g. glycerol or sorbitol], at high temperature under an inert atmosphere with continuous agitation, e.g. in a stainless steel reactor, to effect trans-esterification, e.g. glycerolysis, glycolysis or sorbitolysis. Ingredients (b+c) thus comprise mixtures of mono-, di- and tri-glycerides (i.e. glycerol mono-, di- and tri-esters) with [[( ]]generally minor amounts [[ )]] of free glycerol.

Please replace the first complete paragraph on page 17 with the following amended paragraph:

When present, component (d) suitably comprises a trans-esterification product of a natural vegetable oil triglyceride and a polyalkylene polyol. Such trans-esterification products are known from the art and may be obtained e.g. in accordance with the general procedures described in US Patent No. 3,288,824. They include transesterification products of various natural (e.g. non-hydrogenated) vegetable oils for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil and palm oil and mixtures thereof with polyethylene glycols, in particular polyethylene glycols having an average molecular weight of from 200 to 800. Preferred components (d) are trans-esterification products obtained from maize oil. Further preferred as (d) are products obtained by trans-esterification product of the class defined are commercially available from Etablissement Gattefossé, Boulogne sur Seine, France under the trade name Labrafil [see Fiedler, loc. cit., page 539]. A preferred component (d) is the product

Labrafil M 2125 CS, a ~~plyoxyethylated~~ polyoxyethylated, maize oil having an acid no. = ca. 2, a saponification no. = ca. 155-175 and an iodine no. = ca. 90-100.

Please replace the last paragraph that begins on page 17 and ends on page 18 with the following amended paragraph:

Examples of suitable components (c) for use as (d) include any of those described under (c.1) to (c.6) below. Especially preferred components (c) for use as (d) comprise products obtained by esterification of from about 50 to 75, e.g. about 60, parts by weight of ~~capric~~ caproic acid with glycerol, and comprising, or consisting mainly or essentially of caprylic/~~capric~~ caproic acid mono-and di-glycerides. Especially preferred products of this class are those available under the trade name Imwitor as described under (c.1) below, in particular the product Imwitor 742.

Please replace the third complete paragraph on page 19 with the following amended paragraph:

When (d) is present and is a trans-esterification product of a natural vegetable oil triglyceride and a polyalkylene ~~plyol~~ polyol (for example a Labrafil), (d) is suitably present in an amount of up to about 50%, preferably from about 20 to about 40%, most preferably about 30%, based on the total weight of the composition.

Please replace the third paragraph that begins on page 24 and ends on page 26 with the following amended paragraph:

Examples of suitable components (e') in the compositions as defined under C. above are:

e'.1 Reaction products of a natural or hydrogenated castor oil and ethylene oxide. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil with ethylene oxide, e.g. in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable are the various liquid tensides available under the trade name Cremophor. Particularly suitable are the products Cremophor RH 40 having a saponification number of ca. 50-60, an acid number <1, an iodine number <1, a water content (Fischer) <2%, an n_D^{60} of ca. 1,453 – 1,457 and an HLB of ca. 14 – 16; Cremophor RH 60 having a saponification number of ca. 40 – 50, an acid number <1, an iodine number <1, a water content (Fischer) 4.5-5.5%, and an n_D^{25} of ca. 1.453-1.457 and an HLB of ca. 15-17; and Cremophor EL having a molecular weight (by steam osmometry) of ca. 1630, a saponification number of ca. 65-70, an acid number of ca. 2, an iodine number of ca. 28-32 and an n_D^{25} of ca. 1.471. Also suitable for use in this category are the various tensides available under the trade name Nikkol, e.g. Nikkol HCO-40 and HCO-60. The said product Nikkol HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid value ca. 0.3; saponification number of ca. 47.4; hydroxy value of ca. 42.5; pH (5%) of ca. 4.6; color APHA = ca. 40; m.p. = ca. 36.0°C; freezing point = ca. 32.4°C; H_20 content (%, KF) = 0.03.

e'.2 Polyoxyethylene-sorbitan-fatty acid esters, e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters, e.g. of the type known and commercially available under the trade name Tween (c.f. Fiedler, "Lexikon der Hilfstoffe", 2nd revised and expanded edition (1981), Vol. 2, p.p. 972-975) including the products Tween 20 [polyoxyethylene(20)sorbitanmonolaurate],

40 [polyoxyethylene(20)sorbitanmonopalmitate],

60 [polyoxyethylene(20)sorbitanmonostearate],

65 [polyoxyethylene(20)sorbitantristearate],

85 [polyoxyethylene(20)sorbitantrioleate],

21 [polyoxyethylene(4)sorbitanmonolaurate],

81 [polyoxyethylene(5)sorbitanmonooleate].

Especially preferred products of this class for use in the compositions of the invention are the above products of Tween 40 and Tween 80.

e'.3 Polyoxyethylene fatty acid esters, for example polyoxy- ethylene stearic acid esters of the type known and commercially available under the trade name Myrj (c.f. Fiedler, loc. cit., 1, p.228); an especially preferred product of this class for use in the compositions of the invention is the product Myrj 52 having a D^{25}= ca. 1.1., m.p. = ca. 40-44°C, an HLB value = ca. 16.9., an acid value = ca. 0-1 and a saponification no. = ca. 25-35.

e'.4 Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, e.g. of the type known and commercially available under the trade names Pluronic, Emkalyx and Poloxamer (c.f. Fiedler, loc. cit., 2, p.p. 720-723). An especially preferred product of this class for use in the compositions of the invention is the product Pluronic F68, having an m.p. = ca. 52°C and a molecular weight of ca. 6800-8975. A further preferred product of this class for use in the compositions of the invention is the product Poloxmer 188.

e'.5 ~~Diotylsuccinate~~ Dioctylsuccinate or di-[2-ethylhexyl]-succinate (c.f. Fiedler, loc. cit., 1, p.p. 307).

e'.6 Phospholipids, in particular lecithins (c.f. Fiedler, loc. cit., 2, p.p. 559-560). Lecithins suitable for use in the compositions of the invention include, in particular, soya bean lecithins.

e'.7 Propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate (also known and commercially available under the trade name Miglyol 840), propylene glycol isostearate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth (c.f. Fiedler, loc. cit., 2, p.p. 760 et seq.).

e'.8 Sodium lauryl sulfate.

Please replace the second complete paragraph on page 30 with the following amended paragraph:

Components (c) as aforesaid include both symmetric mono- and di-glycerides (i.e. β-monoglycerides and α,α^1-diglycerides) as well as ~~assymmetric~~ asymmetric mono- and di-glycerides (i.e. α-monoglycerides and a, β-diglycerides) and acetylated derivatives thereof. They also include both uniform glycerides (i.e. in which the fatty acid constituent is composed primarily of a single fatty acid) as well as mixed glycerides (i.e. in which the fatty acid constituent is composed of various fatty acids and acetylated derivatives thereof.

Please replace the first complete paragraph on page 42 with the following amended paragraph:

The compositions obtained in accordance with examples 1 to 7 are suitable for administration for the prevention of transplant rejection or in the treatment of auto-immune disease, e.g. on administration of from 1 to 5 unit dosages, e.g. capsules, daily. Equivalent ~~composition~~ compositions may be prepared substituting any other Cyclosporin, e.g. $[Nva]^2$-Ciclosporin, as component (a) in the same or equivalent amount.

Please replace the third paragraph on page 30 with the following amended paragraph:

Complete physical examination and EcG is performed pre- and post-trial. The following parameters are evaluated within 1-month periods pre- and post-trial:

Blood: - red blood cell count, hemoglobin, hematocrit, erythrocyte sedimentation, white blood cell count, smear, platelet count and fasting glucose;

Serum/plasma – total protein and electrophoresis, cholesterol, triglycerides, Na^{+}, K^{+}, Fe^{++}, Ca^{++}, Cl^{-} creatinine, urea, uric acid, SGOT, SGPT, ~~GT~~ GT-II, alkaline phosphatase, total bilirubin, α-amylase; Urine – pH, microalbumin, glucose, erythrocytes, ketone bodies, sediment.

Cretinine clearance is also determined 1-month prior to trial entry.